

Table SI. Partial clinical trial results of CDK4/6 inhibitors.

A, CDK4/6 inhibitor with AI							
Trial	CDK4/6 inhibitor	Endocrine treatment	Total number of patients	Median PFS in combined therapy group, months	Median OS in combined therapy group, months	Reported HR for PFS	Reported HR for OS
PALOMA-2	Palbociclib	Letrozole	444	24.8	Not reported	HR 0.58 (95% CI 0.46-0.72)	Not reported
MONALEESA-2	Ribociclib	Letrozole	334	25.3	63.9	HR 0.57 (95% CI 0.46-0.70)	HR 0.76 (95% CI 0.63-0.93)
MONARCH-3	Abemaciclib	Letrozole or anastrozole	328	28.2	Not reported	HR 0.54 (95% CI 0.42-0.70)	Not reported
B, CDK4/6 inhibitor with fulvestrant							
Trial	CDK4/6 inhibitor	Endocrine	Total	Median PFS	Median OS in	Reported HR	Reported HR

		treatment	number of patients	in combined therapy group, months	combined therapy group, months	for PFS	for OS
PALOMA-3	Palbociclib	Fulvestrant	347	9.5	34.9	HR 0.46 (95% CI 0.36-0.59)	HR 0.81 (95% CI 0.64-1.03)
MONALEESA-3	Ribociclib	Fulvestrant	484	20.5	53.7	HR 0.59 (95% CI 0.48-0.73)	HR 0.72 (95% CI 0.59-0.90)
MONARCH-2	Abemaciclib	Fulvestrant	446	16.9	46.7	HR 0.54 (95% CI 0.45-0.65)	HR 0.76 (95% CI 0.61-0.95)

AI, aromatase inhibitor; CDK, cyclin-dependent kinase; CI, confidence interval; HR, hazard ratio; OS, overall survival; PFS, progression-free survival.

Table SII. Drugs in clinical trials.

First author, year	Drug	Stage of development	Type of tumor	Trial identifier	(Refs.)
Bisi, 2017	Lerociclib (G1T38)	Phase II	ER ⁺ breast cancer, NSCLC	NCT02821624, NCT02983071	(81)
Profitós-Pelejá, 2023	Narazaciclib (ON123300)	Phase I/II	MCL	NCT06351644, NCT05705505	(82)
Freeman-Cook, 2021	PF-06873600	Phase I	HR ⁺ /HER2 ⁻ breast cancer, metastatic TNBC or advanced cisplatin-resistant epithelial ovarian/fallopian tube cancer	NCT03519178	(83)
Liu, 2019	ETH-155008	Phase I	AML	NCT05758610, NCT04840784	(84)
Carlino, 2018	AMG925 (FLX925)	Phase I	AML	NCT02335814	(80)

AML, acute myeloid leukemia; ER, estrogen receptor; HR, hormone receptor; MCL, mantle cell lymphoma; NSCLC, non-small cell lung cancer; TNBC, triple-negative breast cancer.

Table SIII. Clinical studies of CDK4/6 inhibitors.

Inhibitor	Other drugs	Stage of development	Patients	Objectives of the study	Trial identifier	(Refs.)
Palbociclib or ribociclib		Phase III	Patients with HR ⁺ /HER2 ⁻ metastatic breast cancer	To investigate CDK4/6 inhibitor dosing regimens for patients ≥65 years of age with metastatic breast cancer	NCT06377852	
Palbociclib, ribociclib and abemaciclib	Letrozole	Phase II	Patients with advanced ER ⁺ /HER2 ⁻ breast cancer	To compare the immunomodulatory effects of palbociclib, ribociclib, abemaciclib and letrozole in the neoadjuvant treatment of ER ⁺ /HER2 ⁻ early breast cancer	NCT05766410	

Abemaciclib	Placebo	Phase II	Patients with WHO grade 3 meningioma	To understand how the investigational drug abemaciclib can treat patients with newly diagnosed grade 3 meningioma	NCT05940493	
Palbociclib	Heat shock protein 90 inhibitor TAS-116	Phase I	Patients with refractory solid tumors and Rb deficiency	To evaluate the safety and efficacy of TAS-116 versus palbociclib in the two groups	NCT05655598	
SPH4336		Phase II	Patients with dedifferentiated liposarcoma	To evaluate the safety, blood levels (pharmacokinetics) and preliminary antitumor effects of the CDK4/6 inhibitor	NCT05580588	

				SPH4336 in patients with selected types of liposarcoma (tumors expressing the investigational drug target)		
Trilaciclib	Cyclophosphamide and doxorubicin	Phase II	Patients with TNBC	To evaluate the mechanism of action, as well as the safety and efficacy of trilaciclib in combination with standard of care treatment in the neoadjuvant setting of early-stage TNBC	NCT05112536	
Trilaciclib	Docetaxel and	Phase II	Patients with	To evaluate the effect	NCT04863248	

	placebo		metastatic non-small-cell lung cancer	of trilaciclib on overall survival in patients with metastatic non-small cell lung cancer treated with second - or third-line therapy before administration of docetaxel		
Trilaciclib	Placebo, gemcitabine and carboplatin	Phase III	Patients with TNBC	To evaluate the safety and efficacy of trilaciclib versus placebo administered prior to gemcitabine and carboplatin in patients receiving first- or second-line	NCT04799249	(86)

				treatment for locally advanced unresectable/metastatic TNBC		
Abemaciclib		Phase II	Patients with atypical neurofibroma associated with NF1	To find a safe and tolerable dose of abemaciclib for the treatment of atypical neurofibroma	NCT04750928	
Trilaciclib	Placebo	Phase III	Patients with metastatic colorectal cancer	To evaluate the effect of trilaciclib on osteocyte preservation and antitumor efficacy	NCT04607668	(87)
Abemaciclib		Phase II	Patients with metastatic castration-resistant prostate cancer	To assess the safety and efficacy of abemaciclib	NCT04408924	

HS-10342		Phase I	Patients with solid tumors	To investigate the safety/tolerability and pharmacokinetics of HS-10342 in patients with advanced solid tumors	NCT04060511	
Abemaciclib		Phase II	Patients with neuroendocrine tumors of the digestive system	To evaluate the efficacy of abemaciclib in the treatment of patients with digestive system neuroendocrine tumors	NCT03891784	
G1T38	Osimertinib	Phase Ib/II	Patients with EGFR mutation-positive metastatic NSCLC	To investigate the potential clinical benefit of G1T38 in combination with osimertinib in patients	NCT03455829	

				with EGFR mutation-positive metastatic NSCLC		
Abemaciclib		Phase II	Patients with advanced solid tumors of non-breast origin	Targeted therapies were studied, with abemaciclib used to treat patients with genetic abnormalities (including CCND1, CCND2, CCND3, CDK4 or CDK6)	NCT03310879	
Abemaciclib		Phase I	Advanced or metastatic cancer	To investigate the safety of abemaciclib in patients with advanced and/or metastatic cancer	NCT02919696	(88)
Palbociclib		Phase II	Patients with	To investigate the	NCT02905318	

			metastatic castration-resistant prostate cancer	effect of palbociclib on prostate cancer		
Ribociclib		Phase I/II	Pediatric patients with non-biopsy-associated DIPG and Rb ⁺ biopsy-associated DIPG and HGG treated with radiotherapy	To study the effect of ribociclib given after radiotherapy	NCT02607124	(89)
Palbociclib		Phase II	Patients with anaplastic oligodendroglioma or oligodendrocyte degenerative disorders	To assess the safety and efficacy of palbociclib in adult patients with oligodendroglioma or recurrent anaplastic oligoastrocytoma with	NCT02530320	

				the activity of the protein Rb preserved		
Trilaciclib (G1T28)	Placebo and topotecan	Phase Ib/IIa	Patients with SCLC	To investigate the potential clinical benefits of trilaciclib in preserving bone marrow and the immune system to reduce chemotherapy-induced myelosuppression and improve antitumor efficacy in patients previously treated for extensive-stage SCLC prior to administration of topotecan	NCT02514447	(90)

Palbociclib	Letrozole	Phase I	Patients with ER ⁺ /HER2 ⁻ breast cancer	To evaluate the pharmacokinetics of palbociclib	NCT02499146	(91)
Ribociclib (LEE011)		Phase I	Patients with WHO grade III or IV glioma	To evaluate the pharmacokinetics and efficacy of ribociclib (LEE011) in patients with recurrent glioblastoma or anaplastic glioma	NCT02345824	(92)
Abemaciclib		Phase II	Patients with relapsed or refractory mantle cell lymphoma	To evaluate the disease control rate of abemaciclib in relapsed or refractory mantle cell lymphoma	NCT01739309	(85)
PD 0332991		Phase I	Patients with relapsed and refractory acute	Timed sequential dosing and	NCT01701375	

			leukemia and high-risk MDS	pharmacodynamic trials of PD 0332991		
--	--	--	-------------------------------	---	--	--

CDK, cyclin-dependent kinase; CCNS, cyclin D; DIPG, diffuse pontine glioma; EGFR, epidermal growth factor receptor; ER, estrogen receptor; HGG, high-grade glioma; HR, hormone receptor; MDS, myelodysplasia; NF1, neurofibromatosis type I; NSCLC, non-small-cell lung cancer; Rb, retinoblastoma; SCLC, small cell lung cancer; TNBC, triple-negative breast cancer; WHO, World Health Organization.

Table SIV. Ongoing clinical trials of combination therapy with CDK4/6 inhibitors and immune checkpoint inhibitors.

CDK4/6 inhibitors	Immune checkpoint inhibitors	Stage of development	Patients	Objectives of the study	Trial identifier	(Refs.)
Palbociclib	Avelumab	Phase II	Patients with HR ⁺ /HER2 ⁻ metastatic or locally recurrent unresectable invasive breast cancer	To evaluate the activity of fulvestrant alone, fulvestrant and palbociclib, or a combination of fulvestrant, palbociclib and avelumab, in participants with metastatic HR ⁺ /HER2 ⁻ breast cancer	NCT03147287 (PACE)	(176)
	Pembrolizumab	Phase II	Patients with stage	To evaluate	NCT02778685	(171)

			IV metastatic ER ⁺ /HER2 ⁻ breast cancer	pembrolizumab versus endocrine therapy and palbociclib in postmenopausal patients with newly diagnosed stage IV ER ⁺ breast cancer		
	Nivolumab	Phase II	Patients with ER ⁺ /HER2 ⁻ breast cancer	To evaluate the safety and efficacy of palbociclib and anastrozole with or without nivolumab in participants with ER ⁺ /HER2 ⁻ breast cancer	NCT04075604	(177)
	Avelumab	Phase II	Patients with	To evaluate the safety	NCT04841148	

			early-stage ER ⁺ breast cancer	and early efficacy of hydroxychloroquine or avelumab, with or without palbociclib, in patients with early-stage ER ⁺ breast cancer		
	Avelumab	Phase I	Patients with metastatic TNBC	To determine the safest doses and schedule for the combination of palbociclib and avelumab	NCT04360941	
	INCMGA00012	Phase II	Patients with advanced liposarcoma	To study whether combining the study drugs palbociclib and INCMGA00012 is an	NCT04438824	

				effective and safe treatment for advanced liposarcoma		
	Avelumab	Phase I	Patients with recurrent or metastatic HNSCC	To determine whether avelumab, cetuximab and palbociclib slow or prevent cancer progression and if they cause side effects	NCT03498378	(178)
Abemaciclib	Nivolumab	Phase I/II	Patients with recurrent or recurrent/metastatic HNSCC	To explore the safety and feasibility of abemaciclib combined with nivolumab in the treatment of patients with	NCT03655444	

				recurrent/metastatic HNSCC		
	Nivolumab	Phase II	Patients with hepatocellular carcinoma	To evaluate the effectiveness of the combination of nivolumab and abemaciclib for the treatment of hepatocellular carcinoma	NCT03781960	
	Pembrolizumab	Phase I	Patients with NSCLC or breast cancer	To evaluate the safety and efficacy of abemaciclib in combination with pembrolizumab in participants with advanced NSCLC or	NCT02779751	(170,179)

				HR ⁺ /HER2 ⁻ breast cancer.		
	Pembrolizumab	Phase II	Patients with metastatic/recurrent HNSCC	To assess the objective response rate of tumor lesions to abemaciclib in combination with pembrolizumab in patients with metastatic/recurrent HNSCC	NCT03938337	
	Pembrolizumab	Phase II	Patients with locally advanced unresectable or metastatic gastroesophageal adenocarcinoma	To test the combination of abemaciclib with pembrolizumab in patients with locally advanced	NCT03997448	

				unresectable or metastatic gastroesophageal adenocarcinoma		
	LY3300054	Phase I	Patients with advanced refractory solid tumors	To evaluate the safety and tolerability of LY3300054 in participants with advanced refractory solid tumors.	NCT02791334	(180)
	Atezolizumab	Phase I/II	Patients with HR ⁺ /HER2 ⁻ breast cancer	To evaluate the efficacy and safety of multiple immunotherapy-based treatment combinations in patients with	NCT03280563	

				HR ⁺ /HER2 ⁻ breast cancer		
Ribociclib	Spartalizumab	Phase I	Patients with metastatic HR ⁺ /HER2 ⁻ breast cancer or metastatic epithelial ovarian cancer	To study ribociclib in combination with an immunotherapy drug, spartalizumab, as a possible treatment for patients with metastatic HR ⁺ /HER2 ⁻ breast cancer or metastatic epithelial ovarian cancer	NCT03294694	
	Spartalizumab	Phase I	Patients with recurrent and/or metastatic HNSCC	To examine the safety and efficacy of ribociclib and spartalizumab in	NCT04213404	

				patients with recurrent and/or metastatic HNSCC		
	Spartalizumab	Phase I	Patients with esophageal squamous cell carcinoma or gastrointestinal stromal tumor	To investigate the safety, tolerability and preliminary efficacy of combination therapy with either spartalizumab or ribociclib in selected malignancies	NCT04000529	
	Spartalizumab	Phase II	Patients with unresectable or metastatic LAG-3 ⁺ melanoma	To evaluate the efficacy of novel spartalizumab (PDR001) combinations in	NCT03484923	

				previously treated unresectable or metastatic melanoma		
Trilaciclib	Atezolizumab	Phase II	Patients with SCLC	To investigate the potential clinical benefit of trilaciclib in preserving the bone marrow and the immune system, and enhancing antitumor efficacy when administered with carboplatin, etoposide, and atezolizumab therapy in first line treatment for patients with	NCT03041311	(175)

				newly diagnosed extensive-stage SCLC		
--	--	--	--	---	--	--

CDK, cyclin-dependent kinase; ER, estrogen receptor; HNSCC, head and neck squamous cell carcinoma; HR, hormone receptor; NSCLC, non-small-cell lung cancer; SCLC, small cell lung cancer; TNBC, triple-negative breast cancer.

Table SV. Combination therapy with CDK4/6 inhibitors and targeted agents

Target	Drugs	Stage of development	Objective	Trial identifier	(Refs.)
PI3K	Palbociclib and taselesib (isPI3Ki) or pictilisib (isPI3Ki)	Phase Ib	To evaluate the safety, tolerability and efficacy of the PI3K inhibitors taselesib or pictilisib in combination with palbociclib, followed by the addition of fulvestrant in the treatment of PIK3CA-mutated breast cancer	NCT02389842	
	Letrozole, LEE011 (CDK4/6 inhibitor) and BYL719 (isPI3Ki)	Phase II	To evaluate the efficacy of LEE011, BYL719 and letrozole in the treatment of advanced breast cancer	NCT05625087	
	Inavolisib (isPI3Ki),	Phase I	To evaluate the safety and	NCT03006172	(186)

	fulvestrant and letrozole		tolerability of inavolisib as a single oral agent in patients with locally advanced or metastatic PIK3CA-mutated solid tumors, including breast cancer		
	CYH33, fulvestrant, letrozole and palbociclib	Phase Ib	To evaluate the safety and tolerability of CYH33 combined with endocrine therapy with or without palbociclib in patients with PIK3CA-mutated, HR ⁺ /HER2 ⁻ advanced breast cancer	NCT04856371	
AKT	Capivasertib (AKTi), fulvestrant and	Phase Ib/III	To evaluate the efficacy and safety of capivasertib in	NCT04862663	

	palbociclib		combination with CDK4/6 inhibitors and fulvestrant in patients with locally advanced (inoperable) or metastatic HR ⁺ /HER2 ⁻ breast cancer		
	Ipatasertib (AKTi), fulvestrant and palbociclib	Phase II	To evaluate the efficacy of adding ipatasertib to standard care with a CDK4/6 inhibitor plus fulvestrant	NCT04920708	
	Ipatasertib (AKTi), fulvestrant and palbociclib	Phase I	To evaluate the safety and tolerability of ipatasertib with or without palbociclib, either with an aromatase inhibitor or fulvestrant	NCT03959891	
mTOR	Everolimus (mTORi),	Phase III	To compare the efficacy	NCT00863655	(187)

<p>exemestane and everolimus placebo</p>		<p>and safety of exemestane plus everolimus with exemestane plus placebo in postmenopausal women with ER⁺, locally advanced or metastatic breast cancer that was resistant to NSAI</p>		
<p>Ribociclib, everolimus (mTORi) and exemestane</p>	<p>Phase I/II</p>	<p>To determine whether the triple combination of ribociclib, everolimus and exemestane is safe and effective in the treatment of locally advanced/metastatic breast cancer after treatment with a CDK 4/6 inhibitor</p>	<p>NCT02732119</p>	
<p>Palbociclib, everolimus</p>	<p>Phase I/II</p>	<p>To determine the safe and</p>	<p>NCT02871791</p>	<p>(185)</p>

	and exemestane		tolerable dose of palbociclib, everolimus and exemestane in patients with ER ⁺ /HER2 ⁻ advanced breast cancer		
--	----------------	--	---	--	--

AKTi, AKT inhibitor; CDK, cyclin-dependent kinase; ER, estrogen receptor; HR, hormone receptor; NSAI, non-steroidal aromatase inhibitors; isPI3Ki, isomer-specific PI3K inhibitor; mTORi, mTOR inhibitor.